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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07D 487/04, 471/14
A61K 31/495 // (C07D 487/04
C07D 241:00, 235:00)
(C07D 471/14, 241:00, 235:00
C07D 221:00)

A1

(11) International Publication Number: **WO 94/06798**

(43) International Publication Date: 31 March 1994 (31.03.94)

(21) International Application Number: PCT/GB93/01951

(22) International Filing Date: 15 September 1993 (15.09.93)

(30) Priority data:
9219565.0 16 September 1992 (16.09.92) GB

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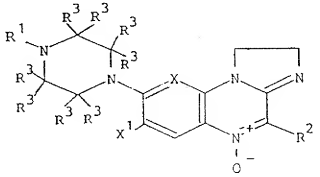
(81) Designated States: AU, JP, KR, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: NOVEL BIOREDUCTIVE COMPOUNDS



(I)

(57) Abstract

A quinoxaline or pyridopyrazine derivative of formula (I) wherein R^1 is a group containing a hydroxyl, oxiranyl, aziridine, alkylamino, pyrrolidino, morpholino, piperidino, piperazino, 2-nitroimidazolyl, or 5-nitrofuryl group; R^2 is a hydrocarbyl or heterocyclyl aromatic group unsubstituted or substituted by one or more substituents selected from halogen, haloalkyl, alkyl, nitro, hydroxy, alkoxy and alkylenedioxy; the groups R^3 are the same or different and each is hydrogen, alkyl, or hydroxy; X is -CH= or -N=, and X^1 is hydrogen or halogen; and pharmaceutically acceptable salts thereof are useful in the treatment of tumours, and in particular hypoxic tumours. Processes for producing the compounds and pharmaceutical compositions containing them.

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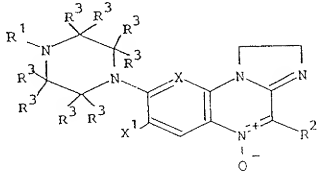
NOVEL BIOREDUCTIVE COMPOUNDS

The present invention relates to dihydroimidazo-quinoxaline and dihydroimidazo-pyridopyrazines useful in the treatment of cancer. It further relates to processes for their preparation and pharmaceutical compositions containing them.

EP-A-214,632 discloses quinoxaline and pyridopyrazine derivatives which are useful as anti-anaerobic agents, for the treatment of diseases related to anaerobic bacteria. Such diseases include for example, post-operative sepsis following lower gastrointestinal surgery or female urinogenital surgery, pelvic inflammatory disease, ulcers, gangrene, trichomonal vaginitis, non-specific vaginitis, amoerbiasis, giardiasis, periodontal disease, acne, and the like.

WO-A-93/00900, which was published after the priority date of the present case, discloses that the compounds disclosed in EP-A-214,632 and pharmaceutically acceptable salts thereof are useful in the treatment of tumours and particularly hypoxic tumours.

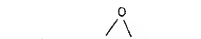
The present invention provides a quinoxaline or pyridopyrazine derivative of formula (I)



(I)

wherein R^1 is a hydroxyalkyl group;

a group of formula (II)



$$-(C(R)_2)_aCR-C(R)_2 \qquad \text{(II)}$$

wherein a is from 1 to 4, the groups R are the same or different and each is hydrogen or alkyl of 1 to 4 carbon atoms such that the group of formula (II) contains in total from 1 to 10 carbon atoms;

a group of formula (III)

$$-R^4-Am \qquad \text{(III)}$$

wherein R^4 is $-(C(R)_2)_b-$ or $-(C(R)_2)_bCROHC(R)_2-$, b is from 1 to 4, the groups R are the same or different and each is hydrogen or alkyl of 1 to 4 carbon atoms, such that R^4 is an alkylene or hydroxyalkylene group containing from 1 to 10 carbon atoms, and Am is alkylamino or dialkylamino or a heterocyclic group which is an aziridino group, unsubstituted or substituted by one or more alkyl substituents or a 1-piperazino group, unsubstituted or substituted in the 2- or 3-position of the piperazine ring by alkyl, hydroxyl or halogen, and in the 4-position of the piperazine ring by an alkyl, cycloalkyl of 5 to 7 carbon atoms, phenyl or pyridyl;

a group of formula (IV)

$$-R^5\text{-}Het^1 \qquad (IV)$$

wherein R^5 is $-(C(R)_2)_c-$ where c is from 1 to 4 or R^5 is $-C(R_2)_dCROH(C(R)_2)_e-$, where d is from 1 to 4, and e is from 1 to 4, at least one of d and e being 1, the groups R are the same or different and each is hydrogen or alkyl of 1 to 4 carbon atoms, such the R^5 is an alkylene or hydroxyalkylene group containing from 1 to 10 carbon atoms, and Het^1 is 2-nitroimidazolyl, optionally further substituted by one or more alkyl, haloalkyl, halogen, hydroxy, alkoxy or nitro substituents; or

a group of formula (V):-

$$-(C(R)_2)_f\text{-}Het^2 \qquad (V)$$

wherein f is from 1 to 6, the groups R are the same or different and each is hydrogen or alkyl of 1 to 4 carbon atoms, such that the group $-(C(R)_2)_f-$ contains from 1 to 10 carbon atoms and Het^2 is a 5-nitrofuryl group, optionally further substituted by one or more alkyl, haloalkyl, halogen, hydroxy, alkoxy or nitro substituents;

R^2 is a hydrocarbyl or heterocyclyl aromatic group unsubstituted or substituted by one or more substituents selected from halogen, haloalkyl, alkyl, nitro, hydroxy alkoxy and alkylenedioxy;

the groups R^3 are the same or different and each is hydrogen, alkyl, or hydroxy;

X is -CH= or -N=, and

X^1 is hydrogen or halogen;

wherein the said alkyl groups and moieties incorporating alkyl groups contain from 1 to 6 carbon atoms unless specified otherwise and the said haloalkyl groups contain one or more halogen atoms;

or a pharmaceutically acceptable salt thereof.

According to further features the present invention provides processes for producing the compounds of the present invention and pharmaceutical compositions comprising them.

In the compounds of formula (I), the alkyl and alkoxy groups may be either straight or branched.

It is preferred that any alkyl groups in the compounds of formula (I) (including alkyl groups which form part of alkoxy groups) be alkyl groups of 1 to 4 carbon atoms, i.e. methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl or tert-butyl. Particularly preferred alkyl substituents are methyl, and ethyl, most preferably methyl.

In the compounds of formula (I) halogen atoms present as halogen substituents or in haloalkyl substituents may for example be fluorine, chlorine or bromine atoms.

In one embodiment of the compounds of the invention R^1 is other than hydroxyalkyl.

Where the group R^1 is a group of formula (II) preferably the groups R are all hydrogen, i.e. the group of formula (II) is unbranched. Where a group R is other than

hydrogen, preferably R is methyl or ethyl, more preferably methyl. Preferably there is no more than one group R which is other than hydrogen. Preferably the group of formula (II) contains from 1 to 8, more preferably 1 to 6 carbon atoms. Preferably a is 1 or 2, more preferably 1.

Where the group R^1 is a group of formula (III), preferably all the groups R are hydrogen, i.e. R^4 is straight chain alkylene or hydroxyalkylene. Where a group R is other than hydrogen, preferably R is methyl or ethyl, more preferably methyl. Preferably there is no more than one group R which is other than hydrogen. Preferably R^4 contains from 1 to 8, more preferably 1 to 6 carbon atoms. Preferably R^4 is a group $-(C(R)_2)_bCROHC(R)_2$ and preferably b is 1 or 2, more preferably 1.

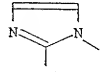
When Am is unsubstituted or substituted, 1-pyrrolidino, 1-piperidino, or 1-morpholino preferably the group is unsubsituted. 1-Morpholino groups are most preferred. When such a group is substituted it is preferably substituted by a single substituent. Preferred substituents include hydroxyl and alkyl, preferably methyl or ethyl, more preferably methyl.

When Am is a 1-piperazino group, preferably the piperazinyl ring is unsubstituted in the 2- and 3-positions. In the 4-position the piperazinyl ring is preferably unsubstituted or N-substituted by alkyl, cyclohexyl or 2-pyridyl, more preferably alkyl and most preferably methyl.

Preferably Am is unsubstituted aziridino. Where Am is substituted aziridino, preferred substituents as methyl and ethyl, more preferably methyl.

Where the group R^1 is a group of formula (IV), preferably the groups R are all hydrogen, i.e. the group R^5 is straight chain alkylene or hydroxyalkylene. Where a group R is other than hydrogen, preferably R is methyl or ethyl, more preferably methyl. Preferably there is no more than one group R which is other than hydrogen. Preferably R^5 contains from 1 to 8, more preferably 1 to 6 carbon atoms. Preferably R^5 is a group $-(C(R)_2)_dCROH(C(R)_2)_e-$, more preferably d and e are the same or different and each is 1 or 2, and still more preferably both d and e are 1. Where R^5 is $-(C(R)_2)_c-$ preferably c is 1 or 2.

Preferably Het^1 is a 2-nitroimidazolyl group, which does not bear any further substituents and most preferably the group of formula (IV) is a group of formula (IVA)

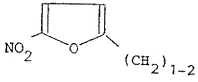


$(CH_2)_{1-2}CHOHCH_2-$ (IVA)

When R^1 is a group of formula (V) preferably the groups R are all hydrogen, so that $-(C(R)_2)_f-$ is straight chain alkylene. Where a group R is other than hydrogen, preferably R is methyl or ethyl, more preferably methyl other than hydrogen. Preferably $-(C(R)_2)_f-$ contains from 1

to 8, more preferably 1 to 6 carbon atoms. Preferably f is 1 or 2.

Preferably the group Het^2 is unsubstituted 5-nitrofuryl (bearing no further substituents) and most preferably the group Het^2 is a group of formula (VA):-



(VA)

In the compounds of formula (I) R^2 may be unsubstituted or substituted, preferably unsubstituted. Hydrocarbyl aromatic groups may for example be phenyl or naphthyl, preferably phenyl and heterocyclyl aromatic groups may for example be pyridyl or thiophenyl, preferably pyridyl. Most preferably R^2 is unsubstituted or substituted phenyl. Pyridyl groups may be 2- or 3-, preferably 3-, pyridyl. Naphthyl groups may be 1- or 2-, preferably 2-, naphthyl. Thiophenyl groups may be 2- or 3- thiophenyl.

Where the group R^2 is substituted it is preferably substituted by 1 or 2 substituents, chosen from halogen, haloalkyl, alkyl, nitro, hydroxy, alkoxy and alkylenedioxy. Preferred substituents include halogen, for example fluorine, chlorine or bromine, haloalkyl, for example trifluoromethyl, nitro, and alkoxy, for example methoxy and ethoxy, preferably methoxy. Where R^2 is substituted phenyl, preferably it is 4-substituted phenyl, more preferably 4-halophenyl and most preferably 4-fluorophenyl.

Preferably each of the groups R^3 is hydrogen. Where R^3 is other than hydrogen, preferably it is hydroxyl or alkyl, preferably ethyl or methyl and more preferably methyl.

In the compounds of formula (I) X is preferably -N=.

Preferably X^1 is hydrogen.

Salts of the compounds of formula (I) may be any pharmaceutically acceptable acid addition salts of the compounds of formula (I). Examples of suitable salts include, salts of inorganic acids such as chlorides, bromides, iodides, phosphates and sulphates and salts of organic acids such as acetates, citrates, lactates and tartrates. Salts of inorganic acids are preferred, hydrochlorides, hydrobromides and hydroiodides are more preferred. Hydrochlorides are most preferred.

Particular examples of the compounds of formula (I) are:-

1,2-Dihydro-8-(piperazin-1-yl)-4-phenylimidazo[1,2-a]quinoxaline 5-oxide,

1,2-Dihydro-8-(piperazin-1-yl)-4-phenylimidazo[1,2-a] pyrido [3,2-e] pyrazine 5-oxide,

1,2-Dihydro-8-((4-oxiranylmethyl)piperazin-1-yl)-4-phenylimidazo[1,2-a] pyrido [3,2-e] pyrazine 5-oxide,

1,2-Dihydro-8-((4-oxiranylmethyl)piperazin-1-yl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide,

1,2-Dihydro-8-(4-(3-(cis-2,3-dimethylaziridinyl)-2-hydroxypropyl)piperazin-1-yl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide,

1,2-Dihydro-8-(4-(3-aziridinyl)-2-hydroxypropyl)piperazin-1-yl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide,

1,2-Dihydro-8-((4-(3-(aziridinyl)-2-hydroxypropyl)piperazin-1-yl)-4-phenylimidazo [1,2-a] quinoxaline 5-oxide,

1,2-Dihydro-8-(4-(3-(2-nitro-1-imidazolyl)-2-hydroxypropyl)piperazinyl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide,

1,2-Dihydro-8-(4-(3-(2-nitro-1-imidazolyl)-2-hydroxypropyl)piperazinyl)-4-phenylimidazo [1,2-a] quinoxaline 5-oxide,

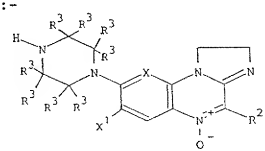
1,2-Dihydro-8-(4-(2-(5-nitrofuryl)methyl)piperazinyl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide, and

1,2-Dihydro-8-(4-(2-hydroxyethyl)piperazinyl)-4-

phenylimidazo [1,2-a]pyrido [3,2-e]pyrazine 5-oxide.

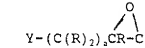
These compounds may be in the form of a free base or of salts, and in particular hydrochloride salts.

Compounds of formula (I) in which R^1 is a group of formula (II) may be prepared by reacting a compound of formula (VI):-



(VI)

in which R^2, R^3, X and X^1 are as hereinbefore defined, with a compound of formula (VII):-

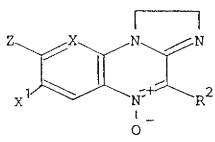


(VII)

where R and a are as hereinbefore defined and Y is a readily displaceable group such as halogen or an alkyl or aryl ester group such as tosylate, mesylate or triflate.

The reaction may be performed in an organic solvent, such as dichloromethane or DMF at ambient temperature.

Compounds of formula (VI) may be obtained by reacting a compound of formula (VIII):-



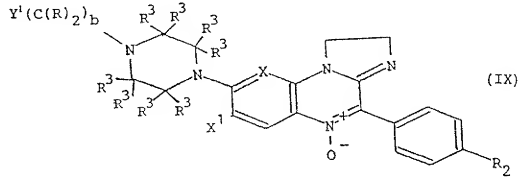
(VIII)

in which R^2, X and X^1 are as hereinbefore defined and Z is halogen, with piperazine or a derivative thereof. This reaction is generally carried out in an organic solvent as reaction medium, such as an alcohol, for example ethanol or propan-2-ol, at a temperature from 60 to 110°C.

Compounds of formula (I) in which R^1 is a group of formula (III) and R^4 is $-(C(R)_2)_bCROHC(R)_2-$ may be obtained by reacting a corresponding compound of formula (I) in which R^1 is a group of formula (II) with an amine Am-H, in which Am is as hereinbefore defined.

The reaction may be performed in an organic solvent, such as an alcohol for example ethanol or 2-propanol, at a temperature from 60 to 110°C.

Compounds of formula (I) in which R^1 is a group of formula (III) and R^4 is $-(C(R)_2)_b-$ may be obtained by reacting an amine Am-H with a compound of formula (IX)



(IX)

wherein X, X, R, R^2, and b are as hereinbefore defined and Y^1 is a readily displaceable group, such as halogen or an alkyl or aryl sulphonate ester group, e.g.,

mesylate, tosylate or triflate.

The reaction may be performed at ambient temperature, in an aprotic solvent, such as DMF, under basic conditions.

Compounds of formula (I) wherein R^1 is hydroxyalkyl may be obtained by conventional methodology from compounds of formula (VI) by reacting with a compound of formula (X)

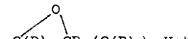
$$Z^2\text{-}(C(R)_2)_b\text{-}OH \qquad (X)$$

wherein Z^2 is halogen, and R and c are as hereinbefore defined. The reaction may be performed in an alcohol, as reaction solvent, for example ethanol or 2-propanol at a temperature from 60 to 110°C.

Alternatively, compounds of formula (I) wherein R^1 is hydroxylalkyl may be obtained by reacting a compound of formula (VIII) as hereinbefore defined with a hydroxyalkyl piperazine. This reaction is generally carried out in an organic solvent as reaction medium, such as an alcohol, for example ethanol or propan-2-ol, at a temperature from 60 to 110°C.

Compounds of formula (I) wherein R^1 is hydroxyalkyl may be converted to a compound of formula (IX), for example by reaction within an alkyl or aryl sulphonic acid at room temperature in basic conditions (to yield a compound in which Y^1 is a sulphonate ester group) optionally followed by reaction with halide, e.g. lithium halide to provide a compound of formula (IX) in which Y^1 is halogen.

Compounds of formula (I) in which R^1 is a group of formula (IV) and R^5 is $-(C(R)_2)_dCROH(C(R)_2)_e-$ and d is 1 may be obtained by reacting a compound of formula (VI) with a compound of formula (XI):-



(XI)

in which Het^1, R and e are as hereinbefore defined.

The reaction may be performed in an organic solvent, such as an alcohol for example ethanol or 2-propanol, at a temperature from 60 to 110°C.

Compounds of formula (XI) in which e is 1 may be prepared using conventional methodology from a halohydroxy compound of formula (XII),

$$Z^3C(R)_2CROHC(R)_2\text{-}Het^1 \qquad (XII)$$

in which Z^3 is halogen and R and Het^1 are as hereinbefore defined. Generally this is performed under basic conditions, eg. using sodium hydroxide as a base.

Compounds of formula (XII) may be obtained by reacting an imidazole Het^1-H with an epichlorohydrin or a derivative thereof of formula (XIII).

$$Z^3C(R)_2CRC(R)_2 \qquad (XIII)$$

in which Z^3 and R are as hereinbefore defined. This may be performed in known and conventional manner.

Compounds of formula (XI) including those where e is not 1 may be prepared alternatively by epoxidation, in conventional manner, e.g. using meta-chloroperbenzoic acid, of a compound of formula (XIV)

$$C(R)_2=CR-(C(R)_2)_e-Het^1 \qquad (XIV)$$

in which R and Het^1 are as hereinbefore defined.

Compounds of formula (XIV) may be obtained by reacting an imidazole Het^1-H with a compound (XV)

$$C(R)_2=CR-(C(R)_2)_e-Z^4 \qquad (XV)$$

in which R is as hereinbefore defined and Z^4 is halogen, in conventional manner.

Compounds of formula (I) in which R^1 is a group of formula (IV) and R^5 is $-(C(R)_2)_dCROH(C(R)_2)_e-$ and e is 1 may be obtained by reacting an imidazolide anion Het^1⁻ with a corresponding compound of formula (I) in which R^1 is a group of formula (II). Preferably the reaction is performed in an aprotic solvent, such as DMF using a salt of the imidazole, such as the potassium salt.

Compounds of formula (I) wherein R^1 is a group of formula (IV) where R^5 is $-(C(R)_2)_e-$ or when R^1 is a group of formula (V), may be obtained by reacting a compound of formula (VI) with a compound of formula (XVI) or (XVII):-

$$Het^1-(C(R)_2)_c-Y^2 \qquad (XVI)$$

$$Het^2-(C(R)_2)_f-Y^2 \qquad (XVII)$$

wherein Het^1, Het^2, R, c and f are as hereinbefore defined and Y^2 is a readily displaceable group such as halogen or an alkyl or aryl sulphonate ester group for example tosylate, mesylate or triflate.

The reaction may for example be performed in basic conditions and in an aprotic organic solvent, for example dichloromethane or DMF, at ambient temperature.

Compounds of formula (I) thus obtained may be purified by chromatography, for example or silica gel, or recrystallised using an appropriate solvent.

Compounds of formula (I) may be converted into pharmaceutically acceptable salts in conventional manner for the formation of acid addition salts. For example, the salts of the present invention may be produced by reaction with an organic acid, or more preferably an inorganic acid such as hydrochloric acid, in an organic reaction medium.

The compounds of formulae (VII), (VIII), (X), (XIII), (XV), (XVI), and (XVII) are compounds which may be prepared using known methods. In particular compounds of formula (VIII) may be prepared according to procedures described in EP-A-214,632.

The compounds of formula (I) and salts thereof are useful in increasing the sensitivity of tumour cells to radiation in radiotherapy and as bioreductive agents. A

compound is administered to a patient having a radiation-reatable cancer, prior to or after, more typically shortly after irradiation of the tumour, in an amount effective to increase the sensitivity of the tumour cells to the effects of the irradiation.

Any solid tumour, which may have regions where cells are radiobiologically hypoxic and become resistant to ionising radiation, may be treated. Examples of such tumours are epithelial tumours of the head, neck, thorax and abdomen, soft tissue sarcomas and brain tumours. The compounds of formula (I) and salts thereof can therefore be employed in the radiotherapy of all such solid tumours where hypoxic cells are known or suspected to exist.

The compounds of formula (I) and salts thereof may also be used where an agent having differential hypoxic cytotoxicity is required. The compounds can be employed for chemopotentiation of a chemotherapeutic agent or as a chemotherapeutic by administration of a compound to a patient having a localised or metastatic cancer. Administration is carried out prior to, simultaneously with or after administration of, typically prior to or simultaneously with, a chemotherapeutic agent such as melphalan, cyclophosphamide, 5-fluorouracil, adriamycin, CCNU(1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea) or tumour necrosis factor (TNF). Any solid tumours, such as above, which are primary or secondary deposits, where it is known or suspected that hypoxic cells are present can

therefore benefit from treatment employing a compound of formula (I) or a salt thereof.

The compounds of formula (I) and salts thereof are useful in particular for the treatment of hypoxic tumours. However they may also be useful in the treatment of other tumours rich in enzymes required to activate them as bioreductive agents or radiosensitisers. Such enzymes may include cytochrome P450, NADPH dependent cytochrome P450 reductase, DT-diaphorase and xanthine oxidase.

The compounds of formula (I) and salts thereof may be administered orally or parenterally. The amount administered depends on factors such as the cancer, the condition of the patient and the body weight of the patient. Typically, however, doses of 50 to 1000mg/m^2 of a patient's body area may be employed.

Accordingly, the present invention further provides a pharmaceutical composition comprising a compound of formula (I), as hereinbefore defined or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier or diluent.

The compounds of formula (I) and salts thereof may be formulated in a manner appropriate to the treatment for which it is to be used by bringing it into association with a pharmaceutically acceptable carrier or diluent. Preferably the composition is in a form suitable for parenteral administration. The compound may be included in a dosage form suitable for bolus injection or such as a

tablet or capsule, for example a capsule comprising known formulation components. The compound may also be formulated for intravenous administration e.g. in a saline drip solution.

Suitable carrier or diluent materials for inclusion in the compositions of the present invention include organic or inorganic inert carrier or diluent material for example, water, gelatin, lactose, starch, magnesium stearate, talc, vegetable oils, gum arabic, polyalkylene-glycols, petroleum jelly and the like. The pharmaceutical compositions may be sterilised, pyrogen-free and isotonic. The compositions may contain adjuvants such as preserving, stabilising, wetting or emulsifying agents, salts for varying the osmotic pressure or buffers. The pharmaceutical compositions may contain other therapeutically valuable substances.

The present invention further provides compounds of formula (I), as hereinbefore defined, and pharmaceutically acceptable salts thereof for use in the treatment of the human or animal body in a method of therapy and the use of compound of formula (I) and pharmaceutically acceptable salts thereof in the manufacture of a medicament for use in the treatment of a tumour, for example a hypoxic tumour.

The following Examples illustrate the invention.

REFERENCE - EXAMPLE 1

1,2-Dihydro-8-(piperazin-1-yl)-4-phenylimidazo[1,2-a]quinoxaline 5-oxide.

Under an argon atmosphere, 1,2-dihydro-8-fluoro-4-phenylimidazo [1,2-a] quinoxaline 5-oxide (4.0g, 14.2 mmol) and piperazine (12.2g, 0.142 mmol) were heated at 90°C in 2-propanol (20 ml) for 3.5h. The solvent was removed under reduced pressure and the residue dissolved in CH_2Cl_2 (50 ml), washed with H_2O (50 ml)) and dried ($MgSO_4$) and concentrated. The resulting orange solid was recrystallised from $EtOAc/CH_2Cl_2$ to yield 4.2g (72%) of 1,2-dihydro-8-(piperazine-1-yl)-4-phenylimidazo[1,2 a]quinoxaline 5-oxide, mp-212-214°C (Found : C; 68.2, H; 6.0, N; 19.6%, $C_{20}H_{21}N_5O.0.33H_2O$ requires C; 68.0, H; 6.1, N; 19.8%).

1,2-Dihydro-8-fluoro-4-phenylimidazo[1,2-a]quinoxaline 5-oxide may be prepared as disclosed in EP-A-214632.

Reference - EXAMPLE 2

1,2-Dihydro-8-(piperazin-1-yl)-4-phenylimidazo[1,2-a] pyrido [3,2-e] pyrazine 5-oxide.

1,2-Dihydro-8-chloro-4-phenylimidazo[1,2-a] pyrido [3,2-e] pyrazine 5-oxide (0.1g, 0.335 mmol) and piperazine (0.288g, 3.35 mmol) were heated at 60°C in 2-propanol for 0.5h under an argon atmosphere. The solution was cooled, evaporated and redissolved in 50ml CH_2Cl_2, washed with H_2O

(50 ml), dried and evaporated to afford, after recrystallisation from EtOAc/$CHCl_3$ 1,2-dihydro-8-(piperazin-1-yl)-4-phenylimidazo[1,2-a] pyrido [3,2-e] pyrazine 5-oxide (72%) as an orange solid, mp=177-178°C (Found : C; 64.7, H; 5.7, N; 23.8%, $C_{19}N_{20}N_6O.0.33H_2O$ requires C; 64.4, H; 5.8, N; 23.7%)

1,2-Dihydro-8-chloro-4-phenylimidazo[1,2-a]quinoxaline 5-oxide may be prepared as disclosed in EP-A-214632.

EXAMPLE 3

1,2-Dihydro-8-((4-oxiranylmethyl)piperazin-1-yl)-4-phenylimidazo[1,2-a] pyrido [3,2-e] pyrazine 5-oxide.

Glycidyl tosylate (1.0g, 4.4 mmol) was stirred in 10 ml anhydrous DMF with 1,2-dihydro-8-piperazin-1-yl)-4-phenylimidazo[1,2-a] pyrido [3,2-e] pyrazine 5-oxide (1.5g, 4.3 mmol), together with 1.5 ml Et_3N for 24h at ambient temperature. The solvent was removed under reduced pressure at 35°C and the residue purified on silica, eluting with MeOH. The resulting solid was recrystallised from 2-propanol to afford 1,2-dihydro-8-((4-oxiranylmethyl)piperazin-1-yl)-4-phenylimidazo[1,2-a] pyrido [3,2-e] pyrazine 5-oxide (55%) as orange crystals, mp=104-107°C, ^{1}H-NMR ($CDCl_3$) δ 2.3 (t,2H,J=6Hz), 2.8 (m,6H), 3.5 (m,4H), 4.1 (s,4H), 6.1 (d,1H,J=2.4Hz), 6.6 (dd,1H,J=2.4 and 9.6Hz), 7.3 (m,3H), 7.8 (m,2H) and 8.1 (d,1H,J=8.4Hz) ppm. (Found : C; 66.7, H; 6.4, N; 16.7%,

$C_{23}H_{23}N_3O_2.0.5H_2O$ requires C; 66.8, H; 6.3, N; 16.9%).

EXAMPLE 4

1,2-Dihydro-8-((4-oxiranylmethyl)piperazin-1-yl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide

This compound was prepared in accordance with the procedure of Example 3 to yield 1,2-dihydro-8-((4-oxiranylmethyl)piperazin-1-yl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide (60%) as an orange solid, mp=196-197°C, ^{1}H-NMR ($CDCl_3$) δ 2.4 (t,2H,J=6Hz), 2.7 (m,7H), 3.8 (m,4H), 4.1 (s4H), 6.2 (d,1H,J=8.4Hz), 7.4 (m,3H), 7.8 (m,2H) and 8.2 (d,1H,J=8.4Hz) ppm.

EXAMPLE 5

1,2-Dihydro-8-(4-(3-(cis-2,3-dimethylaziridinyl)-2-hydroxypropyl)piperazin-1-yl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide

1,2-Dihydro-8-((4-oxiranylmethyl)piperazin-1-yl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide (0.25g, 0.62 mmol) was dissolved in 1.5 ml EtOH (1% Et_3N) together with cis-2,3-dimethylaziridine (0.25 ml, ca. 5 mmol), and the reaction mixture heated under reflux for 3h. The solution was cooled and evaporated, and the residue purified on silica, eluting with $CHCl_3$/MeOH/Et_3N (90:9:1) to give 1,2-dihydro-8-(4-(3-(cis-2,3-dimethylaziridinyl)-2-hydroxypropyl)piperazin-1-yl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide (52%) as orange crystals,

mp=73-76°C, ^{1}H-NMR ($CDCl_3$) δ 1.1 (d,6H,J=4.8Hz), 1.45 (m,2H), 2.4-2.8, (m,8H), 3.5 (m,5H), 4.1 (s,4H), 6.2 (d,1H,J=8.4Hz), 7.35 (m,3H), 7.7 (m,2H) and 8.1 (d,1H,J=8.4Hz) ppm.

EXAMPLE 6

1,2-Dihydro-8-(4-(3-aziridinyl)-2-hydroxypropyl)piperazin-1-yl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide

This compound was prepared in accordance with the procedure of Example 5 but using aziridine and with a reaction time of 0.3h. The residue obtained after evaporation of the solvents was purified on neutral alumina, eluting with MeOH/Et_3N (99:1) to give 1,2-dihydro-8-((4-(3-aziridinyl)-2-hydroxypropyl)piperazin-1-yl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide (35%) as an orange waxy solid ^{1}H-NMR ($CDCl_3$) δ 1.3 (m,2H), 1.8 (m,2H), 2.5-2.8 (m,8H), 3.5 (m,1H), 3.6 (m,4H), 4.15 (s,4H), 6.2 (d,1H,J=8.4Hz), 7.4 (m,3H), 7.8 (m,2H) and 8.2 (d,1H,J=8.4Hz) ppm.

EXAMPLE 7

1,2-Dihydro-8-((4-(3-(aziridinyl)-2-hydroxypropyl)piperazin-1-yl)-4-phenylimidazo [1,2-a] quinoxaline 5-oxide

This compound was prepared in accordance with the procedure of Example 6 using 1,2-dihydro-8-((4-

oxiranylmethyl)piperazin-1-yl)-4-phenylimidazo[1,2-a] pyrido [3,2-e] pyrazine 5-oxide as starting material to afford 1,2-dihydro-8-(4-(3-(aziridinyl)-2-hydroxypropyl)piperazin-1-yl)-4-phenylimidazo [1,2-a] quinoxaline 5-oxide (32%) as an orange solid, mp=124-128°C, ^{1}H-NMR ($CDCl_3$) δ 1.2 (m,2H), 1.8 (m,2H), 2.2-2.5 (m,8H), 3.3 (m,5H), 4.0 (s,4H), 6.0 (d,1H,J=2.4Hz), 6.6 (dd,1H,J=2.4 and 9.6Hz), 7.3 (m,3H), 7.7 (m,2H) and 8.1 (d,1H,J=8.4Hz) ppm.

EXAMPLE 8

1,2-Dihydro-8-(4-(3-(2-nitro-1-imidazolyl)-2-hydroxypropyl)piperazinyl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide

1-Oxiranylmethyl-2-nitroimidazole (0.15g, 0.88 mmol) and 1,2-dihydro-8-(piperazin-1-yl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide (0.15g, 0.43 mmol) were refluxed for 1.5h in 5mL EtOH. The cooled solution was evaporated and purified on silica, eluting with MeOH/$CHCl_3$ (1:9) to give 1,2-dihydro-8-(4-(3-(2-nitro-1-imidazolyl)-2-hydroxypropyl)piperazinyl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide (68%) as an orange solid, mp=158-160°C (dec.), ^{1}H-NMR ($CDCl_3$) δ 2.5 (m,2H), 2.6 (m,4H), 3.55 (m,4H), 4.1 (s,4H), 4.5 (m,3H), 6.3 (d,1H,J=8.4Hz), 7.2 (s,1H), 7.25 (s,1H), 7.3 (m,3H), 7.8 (m,2H) and 8.2 (d,1H,J=8.4Hz) ppm. The product was converted to a bishydrochloride by dissolving in EtOAc/CH_2Cl_2, and treating

with 1.0M HCl in Et_2O. The resulting solid was triturated and washed with Et_2O, to yield the bishydrochloride as an orange solid, mp=>200°C (dec.), (Found : C; 45.2 H; 5.3, N; 18.7%, $C_{25}H_{28}N_9O_4.2HCl.4H_2O$ requires C; 45.3, H; 5.7, N; 19.0%).

EXAMPLE 9

1,2-Dihydro-8-(4-(3-(2-nitro-1-imidazolyl)-2-hydroxypropyl)piperazinyl)-4-phenylimidazo [1,2-a] quinoxaline 5-oxide

This compound was prepared in accordance with the procedure of Example 8 to afford 1,2-dihydro-8-(4-(3-(2-nitro-1-imidazolyl)-2-hydroxypropyl)piperazinyl)-4-phenylimidazo [1,2-a] quinoxaline 5-oxide (69%), as an orange crystalline solid, mp=220-221°C (dec.), (Found : C; 59.4, H; 5.4, N; 21.0%, $C_{26}H_{28}N_8O_4.0.5H_2O$ requires C; 59.4, H; 5.5, N; 21.3%).

EXAMPLE 10

1,2-Dihydro-8-(4-(2-(5-nitrofuryl)methyl)piperazinyl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide

5-Nitrofuran-2-methanol (0.5g, 3.5 mmol) in 2 ml anhydrous CH_2Cl_2 was added slowly with stirring at 0°C to 4-toluenesulphonyl chloride (3.3g, 17.5 mmol) in 3 ml anhydrous CH_2Cl_2 containing Et_3N (0.4g, 5.25 mmol). The solution was stirred for 2.5h and then allowed to reach room temperature, diluted with 50 ml CH_2Cl_2 and washed with 2 x 50 ml H_2O. The solvent was removed under reduced

pressure and the residue purified on silica, eluting with CH_2Cl_2 to afford 0.35g (34%) of 5-nitrofuran-2-methyl 4-toluenesulphonate as a white solid, mp=97-98°C, ^{1}H-NMR ($CDCl_3$) 2.4 (s,3H), 5.0 (s,2H), 6.55 (d,1H,J=4Hz), 7.1 (d, 1H,J=4H$_3$) 7.3 (d,2H,J=8.4Hz) and 7.7 (d,2H,J=8.4Hz) ppm.

5-Nitrofuran-2-methyl 4-toluenesulphonate (0.25g, 0.85 mmol) was added slowly, with stirring, to a solution of 1,2-dihydro-8-(piperazin-1-yl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide (0.2g, 0.575 mmol) in anhydrous CH_2Cl_2 (2ml) containing Et_3N (0.5 ml). Stirring was continued for 1h, and the solution washed with 2 x 10 ml $NaHCO_3$ (aq), dried (Na_2SO_4) and evaporated. The residue was purified on silica, eluting with MeOH, to afford 1,2-dihydro-8-(4-(2-(5-nitrofuryl)methyl)piperazinyl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide (57%) as a dark orange solid recrystallised from EtOH, mp=107-109°C, ^{1}H-NMR ($CDCl_3$) δ 2.6 (m,4H), 3.7 (m,6H), 4.2 (s,4H), 6.3 (d,1H,J=8.4Hz), 6.5 (d,1H,J=4Hz), 7.4 (m.4H), 7.8 (m,2H) and 8.15 (d,1H,J=8.4Hz) ppm.

EXAMPLE 11

1,2-Dihydro-8-(4-(2-hydroxyethyl)piperazinyl)-4-phenylimidazo [1,2-a]pyrido [3,2-e]pyrazine 5-oxide

8-Chloro-1,2-dihydro-4-phenylimidazo[1,2-a] pyrido [3,2-e] pyrazine 5-oxide (1.0g, 3.4 mmol) and 4-hydroxyethylpiperazine (3.9mL, ca.30mmol) were heated at 90°C in 2-propanol (5mL) for 2h. The solution was colled

to 0°C filtered and the solid washed with cold 2-propanol. The mateial obtained was recrystallised from ethanol to give 1,2-dihydro-8-(4-(2-hydroxyethyl)piperazinyl)-4-phenylimidazo [1,2-a]pyrido [3,2-e]pyrazine 5-oxide as an orange solid, mp 200-201.5°C.

EXAMPLE 12

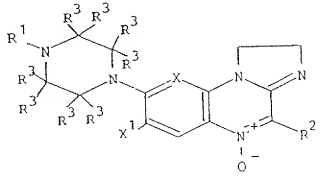
The toxicity of compounds prepared in the foregoing Examples towards aerobic or hypoxic V79 Chinese hamster cells in vitro is shown in Table 1. Toxicity was determined by the use of the modified MTT assay (Stratford and Stephens (1989), Int. J. Radiat. Oncol. Biol. OPhys. 16 973-976). Values quoted represent concentration of drug required to reduce proliferation of treated cultures by 50%. Cells are treated with various drug doses for 3 hours at 37°C under aerobic or hypoxic conditions, following drug removal cells are allowed to proliferate for 3 days prior to assay.

TABLE 1

Compound	C air	C N_2	Ratio
	mmol dm^{-3}		
Example 5	0.05	0.01	5
Example 8	1	0.08	12
Example 9	1.8	0.12	15
Example 11	5.0	0.5	10

CLAIMS

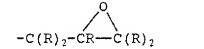
1. A quinoxaline or pyridopyrazine derivative of formula (I)



(I)

wherein R^1 is a hydroxyalkyl group;

a group of formula (II)



(II)

wherein a is from 1 to 4, the groups R are the same or different and each is hydrogen or alkyl of 1 to 4 carbon atoms such that the group of formula (II) contains in total from 1 to 10 carbon atoms;

a group of formula (III)

$$-R^4\text{-Am} \qquad \text{(III)}$$

wherein R^4 is $-(C(R)_2)_b-$ or $-(C(R)_2)_bCROHC(R)_2-$, b is from 1 to 4, the groups R are the same or different and each is hydrogen or alkyl of 1 to 4 carbon atoms, such that R^4 is an alkylene or hydroxyalkylene group containing from 1 to 10 carbon atoms, and Am is alkylamino or dialkylamino or a heterocyclic group which is an aziridino group,

unsubstituted or substituted by one or more alkyl substituents, a 1-pyrrolidino, 1-piperidino, or 1-morpholino group, unsubstituted or substituted by one or more alkyl, hydroxy or halogen substituents or a 1-piperazino group, unsubstituted or substituted in the 2- or 3-position of the piperazine ring by alkyl, hydroxyl or halogen, and in the 4-position of the piperazine ring by an alkyl, cycloalkyl of 5 to 7 carbon atoms, phenyl or pyridyl;

a group of formula (IV)

$$-R^5-Het^1 \qquad (IV)$$

wherein R^5 is $-(C(R)_2)_c-$ where c is from 1 to 4 or $-(C(R)_2)_dCROH(C(R)_2)_e-$ where d is from 1 to 4, and e is from 1 to 4, at least one of d and e being 1, the groups R are the same or different and each is hydrogen or alkyl of 1 to 4 carbon atoms, such the R^5 is an alkylene or hydroxyalkylene group containing from 1 to 10 carbon atoms, and Het^1 is 2-nitroimidazolyl, optionally further substituted by one or more alkyl, haloalkyl, halogen, hydroxy, alkoxy or nitro substituents; or

a group of formula (V):-

$$-(C(R)_2)_f-Het^2 \qquad (V)$$

wherein f is from 1 to 6, the groups R are the same or

different and each is hydrogen or alkyl of 1 to 4 carbon atoms, such that the group $-(C(R)_2)_f-$ contains from 1 to 10 carbon atoms and Het^2 is a 5-nitrofuryl group, optionally further substituted by one or more alkyl, haloalkyl, halogen, hydroxy, alkoxy or nitro substituents;

R^2 is a hydrocarbyl or heterocyclyl aromatic group, unsubstituted or substituted by one or more substituents selected from halogen, haloalkyl, alkyl, nitro, hydroxy, alkoxy and alkylenedioxy;

the groups R^3 are the same or different and each is hydrogen, alkyl, or hydroxy;

X is -CH= or -N=, and

X^1 is hydrogen or halogen

wherein the said alkyl groups and moieties incorporating alkyl groups contain from 1 to 6 carbon atoms unless specified otherwise and the said haloalkyl groups contain one or more halogen atoms;

or a pharmaceutically acceptable salt thereof;

2. A compound according to claim 1 wherein R^1 is a group of formula (III) in which R^4 is $-(C(R)_2)_bCROHC(R)_2-$, and b is 1 or 2.

3. A compound according to claim 2 in which Am is aziridino unsubstituted or substituted by one or more methyl or ethyl groups.

4. A compound according to claim 1 in which R^1 is a group of formula (IV) in which R^5 is $-(C(R)_2)_dCROH(C(R)_2)_e-$ and d and e are the same or different and each is 1 or 2

and Het^1 is 2-nitroimidazolyl.

5. A compound according to claim 1 in which R^1 is a group of formula (V) in which f is 1 or 2 and Het^2 is 5-nitrofuryl.

6. A compound according to any one of the preceding claims wherein R^2 is unsubstituted or substituted phenyl or pyridyl.

7. A compound according to claim 6 in which R^1 is other than hydroxyalkyl.

8. A compound according to claim 6 or 7 wherein R^2 is unsubstituted or substituted phenyl.

9. A compound according to claim 8 wherein R^2 is unsubstituted phenyl or 4-halophenyl.

10. A compound according to any one of the preceding claims wherein all the groups are R^3 are hydrogen.

11. A compound according to any one of the preceding claims wherein X is -N=.

12. A compound according to any one of the preceding claims in which X^1 is hydrogen.

13. A compound according to claim 1 which is

1,2-Dihydro-8-(piperazin-1-yl)-4-phenylimidazo[1,2-a]quinoxaline 5-oxide,

1,2-Dihydro-8-(piperazin-1-yl)-4-phenylimidazo[1,2-a] pyrido [3,2-e] pyrazine 5-oxide,

1,2-Dihydro-8-((4-oxiranylmethyl)piperazin-1-yl)-4-phenylimidazo[1,2-a] pyrido [3,2-e] pyrazine 5-oxide,

1,2-Dihydro-8-((4-oxiranylmethyl)piperazin-1-yl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide,

1,2-Dihydro-8-(4-(3-(cis-2,3-dimethylaziridinyl)-2-hydroxypropyl)piperazin-1-yl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide,

1,2-Dihydro-8-(4-(3-aziridinyl)-2-hydroxypropyl)piperazin-1-yl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide,

1,2-Dihydro-8-((4-(3-(aziridinyl)-2-hydroxypropyl)piperazin-1-yl)-4-phenylimidazo [1,2-a] quinoxaline 5-oxide,

1,2-Dihydro-8-(4-(3-(2-nitro-1-imidazolyl)-2-hydroxypropyl)piperazinyl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide,

1,2-Dihydro-8-(4-(3-(2-nitro-1-imidazolyl)-2-hydroxypropyl)piperazinyl)-4-phenylimidazo [1,2-a] quinoxaline 5-oxide,

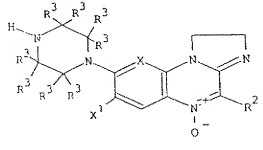
1,2-Dihydro-8-(4-(2-(5-nitrofuryl)methyl)-piperazinyl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide, or

1,2-Dihydro-8-(4-(2-hydroxyethyl)piperazinyl)-4-phenylimidazo [1,2-a]pyrido [3,2-e]pyrazine 5-oxide;

or a pharmaceutically acceptable salt thereof.

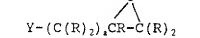
14. A process for producing a compound as claimed in any one of the preceding claims which process comprises:-

where R^1 is a group of formula (II), reacting a compound of formula (VI):-



(VI)

wherein R^2, R^3, X and X^1 are as defined in claim 1 with a compound of formula (VII):-

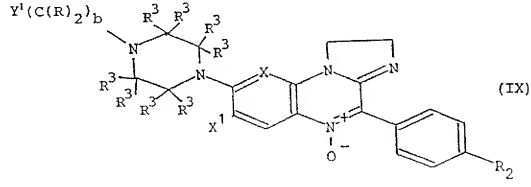


(VII)

where R and a are as defined in claim 1 and Y is a readily displaceable group;

where R^1 is a group of formula (III) and R^4 is $-(C(R)_2)_bCROHC(R)_2-$, reacting a compound of formula (I) in which R^1 is a corresponding compound of formula (I) in which R^1 is a group of formula (II) with an amine Am-H in which Am is as defined in claim 1;

where R^1 is a group of formula (III) and R^4 is $-(C(R)_2)_b-$, reacting an amine Am-H with a compound of formula (IX):



(IX)

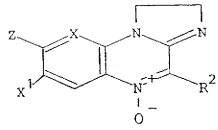
wherein X, X^1, R, R^2 and b are as hereinbefore defined and Y^1 is a readily displaceable group;

where R^1 is hydroxyalkyl, reacting a compound of formula (VI), as hereinbefore defined, with a compound of formula (X)

$$Z^2-(C(R)_2)_b-OH \qquad (X)$$

wherein Z^2 is halogen and R and b are as defined in claims 1;

where R^1 is hydroxyalkyl, reacting a compound of formula (VIII)



(VIII)

in which R^2, X and X^1 are as defined in claim 1 and Z halogen with a hydroxyalkylpiperazine;

where R^1 is a group of formula (IV) in which R^5 is $-(C(R)_2)_dCROH(C(R)_2)_e-$, reacting a compound of formula (VI), as hereinbefore defined, with a compound of formula (XI):-

(XI)

wherein Het^1, R and e are as defined in claim 1;

where R^1 is a group of formula (IV) and R^5 is $-(C(R)_2)_dCROH(C(R)_2)_e-$ and d is 1, reacting an imidazolide anion Het^{1-} with a corresponding compound of formula (I) in which R^1 is a group of formula (II); or

where R^1 is a group of formula (IV) where R^5 is $-(C(R)_2)_e-$ or R^1 is a group of formula (V), reacting a compound of formula (VI), as hereinbefore defined, with a compound of formula (XVI) or (XVII):-

$$Het^1-(C(R)_2)_e-Y^2 \qquad (XVI)$$

$$Het^2-(C(R)_2)_f-Y^2 \qquad (XVII)$$

wherein Het^1, Het^2, R, c and f are as defined in claim 1, and Y^2 is a readily displaceable group; and

optionally, converting the compound of formula (I) thus obtained into a pharmaceutically acceptable salt thereof.

15. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 13 in association with a pharmaceutically acceptable carrier or diluent.

16. A compound as claimed in any one of claims 1 to 13 for use in the treatment of the human or animal body as a method of therapy.

17. Use of a compound as claimed in any one of claims 1 to 13 in the manufacture of a medicament for use in the treatment of a tumour.

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C07D487/04 C07D471/14 A61K31/495 //(C07D487/04,241:00, 235:00),(C07D471/14,241:00,235:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 214 632 (SEARLE) 18 March 1987 cited in the application see example 11	8
P,A	WO,A,93 00900 (BRITISH TECHNOLOGY GROUP) 21 January 1993 cited in the application see claim 1	17

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 December 1993	20. 12. 93

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Alfaro Faus, I

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		JP-A- 62063584	20-03-87
WO-A-9300900	21-01-93	AU-A- 2197892	11-02-93
		GB-A- 2257361	13-01-93